ELSEVIER

Biomed Pharmacother 56 (2002) 223–234

& BIOMEDICINE PHARMACOTHERAPY

Review

# Myeloma aetiology and epidemiology

G.J. Morgan [a,*], F.E. Davies [a], M. Linet [b]

[a] *Molecular Haematology, Academic Unit of Haematology and Oncology, University of Leeds, Leeds, UK*
[b] *Radiation Epidemiology, Division of Cancer Epidemiology and Genetics, National Cancer Institute USA, Bethesda, MD, USA*

Received 15 April 2002; accepted 25 April 2002

**Abstract**

Recently there have been substantial improvements in our understanding of the biology of myeloma. These findings have important implications for aetiological studies aimed at defining the causative factors for myeloma. Myeloma is closely related to monoclonal gammopathy of unknown significance (MGUS), which is now recognized to be very common in the older population. The epidemiology of these conditions is presented and discussed in the context of the genetic factors governing both the risk of developing MGUS or of transformation to myeloma. Biological studies support a role for aberrant class switch recombination early in the natural history of myeloma suggesting that factors in the environment may interact with this mechanism to increase myeloma risk. Case-control and cohort studies have identified several known and suspected environmental exposures. These exposures include high doses of ionizing radiation, and occupational exposure in the farming and petrochemical industries. The data supporting these associations are presented and discussed in the context of the molecular mechanisms underlying these exposures. In particular DNA damage occurring as a consequence could readily interact with the class switch recombination process to increase the risk of chromosomal translocations, oncogene deregulation and malignant transformation. A further hypothesis, which has been extensively investigated, is the role of chronic immune/antigenic stimulation and the risk of myeloma. This concept is difficult to explain in the context of our current immunological concepts. The data supporting the association and how molecular epidemiological studies using genetic variants in cytokine genes are allowing us to revisit this concept are discussed in detail. 

*Keywords:* Myeloma; Epidemiology; Genetics

## 1. Descriptive epidemiology

Multiple myeloma constitutes around 10–15% of all haematological malignancies, 1% of all cancers and has an incidence of around 2/100 000 population in the United Kingdom [33,34]. The incidence increases with age with only approximately 40% of patients presenting under the age of 60 years and 2% of cases occurring before the age of 40 years. Internationally, the incidence of myeloma is highest among African-Americans, followed by Maoris, Hawaiians, Israeli Jews, northern Europeans, US and Canadian whites [20]. Lowest rates occur in the Middle East, Japan, and China [25]. After age 50, incidence rates for multiple myeloma are higher in males than in females among both Caucasians and African-Americans [170]. Population-based incidence rates for monoclonal gammopathy of unknown significance (MGUS) are lacking and population-based prevalence data are limited. The prevalence of MGUS rises with increasing age [6,95,96,125,174]. Similar to multiple myeloma, prevalence rates for MGUS (a disorder characterized by a serum M-protein level less than 3 g/dl, fewer than 10% plasma cells in the bone marrow, and absence or presence of only small amounts of M-protein in the urine) are high in African-Americans (8.4%) mid-level in Caucasian Americans (3.8%) [39,178,187,189], and low in Japanese-Americans [25]. Estimates of the population prevalence of MGUS are based on relatively small samples of elderly patients in health screening studies. These results suggest that racial differences in immunogenetic factors may affect the risk of developing both MGUS and myeloma.

* Corresponding author.
*E-mail address:* garethm@pathology.leeds.ac.uk (G.J. Morgan).


PII: S0753-3322(02)00194-4

Time trends of myeloma have been examined in the UK and the results suggest an annual increase in incidence of under 1% per annum from 1984 to 1993 [34]. International trends have also been extensively investigated [40]. In the US, incidence rates for Caucasians rose 1% per annum during 1973–1991, and subsequently declined about 1.2% per annum, while for African-Americans, the annual increase has been less than 1% per annum during 1973–1997 [170]. An increase of about 2% per annum has been observed in most European countries [154]. In southeast Asia, incidence rates rose rapidly from a very low base rate. In many populations, however, there are some suggestions of a recent levelling off of incidence rates, suggesting that earlier increases in incidence may have reflected improved diagnosis or a cohort effect in the population. Although it may be difficult to retrospectively disentangle a cohort effect that has now passed, with no increase in incidence in those born after the 1930s, from improvements in diagnosis, data from the UK support the latter interpretation [204,221]. A number of clusters of myeloma have been described but the significance of these is uncertain [61,122,125,128].

## 2. Clinical features and biology

In order to understand the factors which are important in the aetiology of myeloma, it is important to consider not only the potential environmental exposures but also consider these in light of the biology of the disease. Multiple myeloma is a clonal B-cell neoplasm of plasma cells. Plasma cells, the final products of B-cell differentiation, synthesize and release immunoglobulins, light and heavy chain subunits of immunoglobulins, and cytokines designated osteoclast activating factors. The clinical picture of myeloma is a complex of bone destruction leading to pain or fracture with hypercalcaemia, infection due to immune deficiency and marrow failure leading to anaemia. Renal failure due to hypercalcaemia, direct damage from paraprotein or precipitation of light chain in renal tubules is also a common feature. The diagnosis requires the presence of at least two of three characteristic features: a paraprotein or monoclonal immunoglobulin in the blood and/or the urine, bone marrow infiltration by malignant plasma cells and the presence of osteolytic bone lesions. Monoclonal gammopathy of uncertain significance (MGUS) is a related disorder characterized by a serum M-protein level less than 3 g/dl, fewer than 10% plasma cells in the bone marrow, and absence or presence of only small amounts of M-protein in the urine. In contrast to cases of myeloma, most patients with MGUS maintain stable levels of M-protein and do not develop clinical manifestations of multiple myeloma [129]. Some, however, progress to the typical picture of myeloma and MGUS is assumed to be the precursor of clinically apparent myeloma with one or more additional genetic events being required for progression to myeloma. Specialty hospital [16,124,155] and population-based hospital studies [87] have shown that 20–25% of patients with MGUS progress during 10- [16,155] or 20-year [124] follow-up periods to clinically apparent of myeloma.

## 3. Cytogenetic analysis

Cytogenetic studies in myeloma are technically difficult but have been very important in delineating the genetic events, which underlie this disorder. Over the last few years, recurrent chromosome translocations in multiple myeloma have been identified in cell lines including t(11;14)(q13;q32), t(4;14)(p16;q32), t(14;16)(q32;q23) and t(6;14)(p25;q32). Cytogenetic techniques such as FISH have shown that rearrangements of the immunoglobulin heavy chain (IgH) locus at 14q32 can occur in up to 74% of cases and are important early events in the molecular pathogenesis of myeloma [8]. The IgH locus is strongly transcriptionally active in B cells and transfer of an oncogene to this region results in dysregulation of the gene in question. Since these rearrangements at the IgH locus on chromosome 14q32 appear to cluster in switch regions, it is thought that aberrant class switch recombination is a central pathogenic mechanism in the majority of myelomas. Conventionally these translocations have been associated with the dysregulation of specific genes, namely, cyclin D1, FGFR3, c-maf and MUM1 (IRF4), respectively, however, it is clear that a promiscuous array of partner loci are implicated.

## 4. IgH mutational analysis

Myeloma plasma cells have a number of characteristic features including abnormal localization within the bone marrow, replacement of normal bone elements and dysregulation of immunoglobulin secretion. There is much debate and controversy, however, regarding the exact site of origin and nature of the proliferating cell. Normal bone marrow plasma cells are derived from cells that have passed through a germinal centre in a lymph node or other organ. Within the germinal centre, cells undergo somatic hypermutation, class switching of the immunoglobulin gene and selection by antigen binding affinity with only cells with high binding affinity surviving to become plasma cells. In myeloma, the immunoglobulin genes from individual plasma cells show the same pattern of hypermutation, consistent with the clonal expansion of a single post-germinal centre B cell. A number of studies have also detected clonal VDJ sequences linked to the μ heavy chain suggesting the presence of a

pre-switched cell as part of the myeloma clone or the presence of a marginal zone memory B cell. This contrasts with the situation in MGUS where there is intra-clonal variation in the pattern of mutation, suggesting that MGUS is the result of transformation of a virgin or memory B cell, the progeny of which continues to pass through the normal process of germinal centre selection before becoming plasma cells.

## 5. A molecular model of myeloma

The relationship of MGUS to myeloma and the shared genetic features between the two conditions allow us to construct a genetic model, which defines a number of distinct stages. These include a possible pre-MGUS stage, MGUS, presenting myeloma, relapsed disease and advanced stage disease with extramedullary disease. The development of such a model combined with an epidemiological approach will allow us to test specific questions relating to the molecular mechanisms involved in the predisposition to and progression of myeloma. It is of particular interest to investigate the role played by mistakes occurring during the normal processes important in B-cell development. These include somatic hypermutation and class switch recombination.

## 6. Genetic effects

There are various lines of evidence, which suggest possible links between genetic predispositions and multiple myeloma [137]. A case-control study has linked multiple myeloma with an excess of degenerative or demyelinating disorders of the central nervous system in first-degree relatives and twins [104,112,145]. There is a 3- to 6-fold elevated risk of myeloma among persons with a history of a first-degree relative with multiple myeloma [24,30,41,63]. Risks of familial occurrence of haematological malignancy may be higher for African-Americans than for Caucasians [30], although more and larger studies are needed to further evaluate this finding. Detailed evaluation of families with two or more cases among first-degree relatives reveals that most cases of familial myeloma occurred among siblings [30,84,89], although this may reflect underdiagnosis among parents, particularly in earlier periods. Several reports of concordant occurrence of myeloma among spouses suggest a possible contributory role for environmental factors [31,114,116,126,127,150,159]. Among index patients with myeloma, risk of other haematological malignancies was also increased [63,186]. Excesses of autoimmune disorders [134] and degenerative central nervous system disorders [90] have also been observed among relatives of myeloma patients [90,113,114,188]. There was an excess of the ABO blood group A in cases [2,66] in one study but not in another. Also a weak association between multiple myeloma and HLA-B5 has been described. The excess of multiple myeloma in the US black population has been interpreted as a sign of possible genetic differences. One study showed that the risk of HLA-Cw2 was higher in the black cases than white, despite the fact that Cw2 is distributed equally between the races; there were also suggestions of a linked association with the DQ locus [162]. There is no obvious excess of myeloma described in any of the inherited immunodeficiency syndromes though this does not totally exclude immunodeficiency as a cause of myeloma.

## 7. Molecular epidemiology

Gene environment interactions are important in the aetiology of many tumours and chronic immune-stimulation has been suggested as a potential aetiological factor in myeloma. Inherited genetic polymorphisms at cytokine loci acting early in the immune response may mediate immune responsiveness and in contrast to factors often evaluated in case-control studies are readily quantifiable using PCR based techniques. There are two main approaches to studying these effects in myeloma. The first is to utilize our understanding of the critical factors in determining the pro-inflammatory response and the TH1/TH2 make up of the immune system. One could then identify for further study highly prevalent genetic variants that exert functional effects on these cytokines. These genetic variants can then be evaluated in population-based, case-control investigations of myeloma, and attributable risks calculated for myeloma. The other approach is to utilize variants in key cytokines known to be involved in the pathogenesis of myeloma, an example of which is IL6.

The first approach is illustrated by the study of variants in TNF. Tumour necrosis factor α (TNFα) and lymphotoxin α LTα, formerly known as tumour necrosis factor β, are two critical cytokines produced early in the inflammatory process. Both cytokines are involved in T cell dependent B-cell responses, T cell proliferation and receptor expression, NK cell activity and dendritic cell maturation. Their role in B-cell development has been shown in studies of knock out mice. TNFα/LTα knock out mice show no germinal centre formation, defects in the regulation of isotype switching and problems with both primary and secondary immune responses. In addition to these normal functions, a number of studies have suggested an important role in the pathogenesis and maintenance of the malignant clone in myeloma.

The TNFα and LTα genes are located on chromosome 6p within the class III region of the MHC locus. Four polymorphic sites within the promoter region of the TNFα gene

and one polymorphic site within the first intron of the LTα gene have been described, two of these seem to have functional significance in vivo. A single base substitution at position –308 of the TNFα gene results in two allelic forms in which the presence of guanine defines the common variant TNF1 and the presence of adenine defines the less common variant TNF2. The polymorphism within the LTα gene also results from a single base substitution in which guanine is replaced by adenine at position +252 of the first intron. The two forms are referred to as LT10.5 and LT5.5, respectively. These two polymorphisms are in linkage disequilibrium and both high-producer alleles are associated with the extended HLA haplotype A1-B8-Dr3-DQ2.

Comparison of the extended TNFα/LTα halotype in myeloma cases and controls showed a significant excess of high-producer alleles in myeloma cases. The double heterozygotes TNF 1/2 and LT 10.5/5.5 were present in 35.8% of cases but in only 18% of controls; this was associated with a 2-fold, significantly increased risk of myeloma [50]. A similar increase in risk was also seen in MGUS cases, suggesting that this genotype is associated with the initiation of plasma-cell disorders rather than with the progression of MGUS to myeloma [50].

The second approach is illustrated by the investigation of variants in the IL6 gene and their association with myeloma risk. IL6 is known to be a central cytokine controlling myeloma cell growth and survival.

The 5' control region of the gene is polymorphic, with a G/C polymorphism at position –174 having functional significance. The C allele results in lower levels of IL6 transcription in cell lines and is associated with significantly lower levels of plasma IL6 in normal individuals [70]. However, two large studies of myeloma cases and controls have found no association between this polymorphism and the development of MGUS or myeloma [60,220].

## 8. Specific epidemiological associations

A substantial number of epidemiological studies have evaluated a range of postulated risk factors. Few consistent associations have been described, however. This review does not attempt to be comprehensive, but instead focus on several, biologically plausible risk factors and delineate the possible biological pathways through which they act. Two exposures of particular interest that have been evaluated in large, methodologically rigorous studies are ionizing radiation and benzene. Statistical associations have also been observed for multiple myeloma among farmers, paper producers, wood workers and workers occupationally exposed to petrochemicals, and materials used in plastic and rubber manufacture. Lifestyle factors linked with elevated risk of myeloma include socio-economic status, smoking, alcohol, diet and hair dyes [1,27-29,36,37,43,74,94,97,110,111,146,192,198,219]. A recurring theme is the association with variation in immune response and this is developed further below.

## 9. Ionizing radiation

Overall the data provide modest support for a relationship between ionizing radiation and an elevated risk of multiple myeloma and its precursor MGUS [45,165]. Associations have been seen in Japanese survivors of the World War II atomic bombs, patients treated with high-dose radiotherapy, and some occupational, radiation-exposed cohorts [68,102-105,135,151,153,158,173,184,200-202]. The classical feature of radiation exposure is the generation of DNA double stranded breaks. Such molecular events could readily interact with the switch recombination machinery to increase the risks of IgH translocations, oncogene deregulation and consequently multiple myeloma. Following exposure to fallout from atomic bombs, a small but significant increased risk was seen with no variation in gender or age at exposure [151,164].

An excess of myeloma deaths was observed among early American radiologists [131], and more recently myeloma risk was reported to be two times higher among radiologists than among physicians in other specialties [109,183]. Yet, no excess of myeloma was found among more than 27,000 Chinese diagnostic X-ray workers during a 30-year period, compared to medical workers unlikely to have had occupational X-ray exposure [205,206].

Risks from occupational exposure in the nuclear industry are small and the evidence conflicting [58,80-82,139,157,160,191,193]. In combined analysis of cancer mortality data for 95,673 nuclear industry workers in the US, the UK and Canada, there was a small but significant 1.9-fold increased risk for multiple myeloma. In a recent follow-up of cancer mortality among 124,743 workers included in the National Registry for Radiation Workers in the United Kingdom, there was some evidence of an increasing trend in risk of multiple myeloma with increasing estimated external radiation dose, although the trend disappeared after the investigators omitted workers monitored for exposure to internal radiation emitters [149].

Evidence for an increased risk of myeloma from military exposure is conflicting. Increases in multiple myeloma mortality and incidence were observed among 21,358 British military men who participated in atmospheric nuclear weapons tests when compared to 22,333 unexposed controls [48]. Yet no excesses occurred in New Zealand military participants in the same nuclear weapons tests [156], nor in US soldiers participating in military manoeuvres at Nevada nuclear weapons test sites [32]. There is little evidence of an

increased risk of multiple myeloma based on comprehensive studies of US and UK populations living in residential proximity to nuclear facilities [9,15,42,78,79,136].

While no association has been found between risk of myeloma and diagnostic X-rays in most case-control [21,46,73] or cohort [23,51] studies, increased risks have been observed in individuals treated therapeutically [51,88,100,104,172,185,190]. Of historic interest was a finding of a significantly increased risk of myeloma and other haematological malignancies among Danish women who had received injections of thorotrast (alpha-emitting X-ray contrast medium) for cerebral arteriography [3,4,140,203]. A small but significantly elevated risk of myeloma was found among a cohort of 14,556 patients with ankylosing spondylitis who received a mean total body dose of 2.64 Gy, with the heaviest dose to the vertebrae [47,207]. Among over 180,000 women treated for cervical cancer, no overall excess risk of myeloma was associated with radiation therapy; however, a trend analysis revealed significantly increased risks after the first 10 years of treatment [22]. In a cohort of 2067 women in Scotland given X-ray therapy for metropathia haemorrhagica, an elevated 2.6-fold standardized mortality ratio was ascertained for multiple myeloma 5 or more years after the women had received a mean bone marrow dose of 1.3 Gy [49].

## 10. Benzene exposure

Despite a coherent molecular mechanism whereby benzene exposure could result in the development of haematological malignancy, it remains one of the most contentious topics in recent years as to whether or not benzene exposure is linked with elevated risk of multiple myeloma [8,14,76,85,177,216-218]. Rinsky et al. [171] described four workers with multiple myeloma and nine with myeloid leukaemia in a population of approximately 1100 workers manufacturing Pliofilm [44]. In an updated study of that population, there was no significant association of benzene exposure with multiple myeloma, although risk of acute myeloid leukaemia rose dramatically with increasing estimated level of benzene, reaching a 98-fold excess among workers with a cumulative exposure of more than 400 ppm-years [59,212]. Among 4172 chemical manufacturing workers exposed to low levels of benzene, a 2.3-fold non-significant excess of multiple myeloma and a similar excess of leukaemia occurred among workers 20 or more years after their first exposure, but no excess was observed among maintenance workers with intermittent high exposure to benzene [106]. Non-significant excesses of multiple myeloma have been found among workers employed in the petrochemical industry or in petrol distribution [53,56,101,152,167,179-181,215]. No excess of myeloma was found in a meta-analysis of data from 22 cohort mortality studies of petroleum workers in the United States, Canada, the United Kingdom, and Australia [213]. However, among a large population of Chinese benzene-exposed workers, no excess of myeloma was seen [93].

## 11. Other environmental exposures and solvents

There are a number of other chemical exposures, which have been investigated including styrene and butadiene. Risks of myeloma have also been evaluated among rubber industry workers [5,52,54,55,67,72,75,92,120,121,147,176,210,214], but overall results do not show evidence of consistently increased risk of myeloma. Dioxins have been suggested to increase risk [64,69,194] in particular for women residing in the exposed region of Seveso and Swedish fishermen [10-12,142,182,197]. A small cohort of Swedish paint industry workers with long-term exposure to organic solvents was reported to have a 4-fold excess risk of multiple myeloma [138]. Other studies have also linked increased risk of myeloma to employment in the paint industry [13,54] and exposure to ethylene oxide [148,195] and styrene [214]. Solvents other than trichloroethylene were linked with slightly increased mortality from myeloma among 14,457 aircraft maintenance workers [17]. An association was observed between chemical industry work and death from multiple myeloma (as well as non-Hodgkin's lymphoma and lymphoid leukaemia) among persons under age 65 at death in a case-control death certificate study of haematopoietic cancers among white male residents of Kanawha County, West Virginia [141].

## 12. Agricultural and related occupational exposure

The majority of epidemiological studies which have evaluated the risk of myeloma among agricultural workers have reported positive associations [18,19,98,117,144,157,163,196,209]. These studies are difficult to interpret because of the multiple potential exposures and marked person-to-person variation. Among 88,090 deceased white male farmers in Iowa, the proportionate mortality ratio was increased for multiple myeloma [35]. A cohort study of 140,208 Swedish farmers showed significantly increased incidence of multiple myeloma, even in those parts of Sweden where the use of pesticides has been less frequent [208]. In a cohort study of 246,104 Norwegian farmers, the incidence of multiple myeloma was significantly elevated among those with indicators of pesticide usage, particularly farmers cultivating potatoes [123]. Among 205,000 workers

on the Farm Register in Finland, multiple myeloma incidence was significantly increased among farmers on pig or poultry farms, but not among those working on other types of farms [166]. A recent meta-analysis of 32 studies published between 1981 and 1996 yielded an overall estimated risk of 1.23 (95% CI = 1.14–1.32) [117]. Significant increases in risk of multiple myeloma were found in workers exposed to dichloro-diphenyl-trichloroethane (DDT) in application or inspection jobs [38]. Other types of pesticide usage by farmers have also been linked with elevated risk of multiple myeloma [19,119,175], as have exposures to grain dusts [77], engine exhausts and fuels [71], and contact with farm animals [65,157]. Particularly with regard to pesticides, numerous studies have investigated the relation between potential exposure and multiple myeloma, with some reporting elevated risks, while others have not [98,169]. Only a few investigations have attempted to examine the role of specific pesticide exposures, but results have been conflicting [26,65,143].

## 13. Immune dysfunction

Immunodeficiency due to AIDS is one of the most common causes of profound immunodeficiency. This could potentially result in myeloma as a consequence of two mechanisms: a direct effect of the human immunodeficiency virus or an indirect effect from a concurrent viral infection. In a large study linking population-based cancer and AIDS registries, a 4.5-fold increased risk of myeloma occurred among people with AIDS [83]. A 12-fold excess of myeloma was found in a register-based retrospective cohort study in Australia [91]. The association of human herpesvirus infections with important cancers arising in AIDS patients has been noted [7]. An association of HHV8 with myeloma has been suggested but was later dismissed [168,199]. Overall there is little evidence to support a direct effect of an infectious organism on risk of myeloma.

The results of induced plasmacytomas in mice [161], clinical reports [107], and limited data from epidemiological studies [169] have led investigators to hypothesize that repeated or chronic antigenic stimulation of the immune system may lead to myeloma. From an immunological perspective, this hypothesis is difficult to justify mechanistically but nonetheless a number of case-control studies have explored this theory. Risk has been evaluated in relation to past history of chronic infections, inflammatory, connective tissue, autoimmune, and allergy-related disorders [99]. Elevated myeloma risks have been suggested for allergic conditions [77,130], musculoskeletal disorders [57], and rheumatoid arthritis [62,108,115]. Weak links were found for past bronchitis and eczema [77,86,130,211] and for scarlet fever, chronic bacterial disease, BCG vaccination and recent shingles infection [118]. But, other studies of individuals with these conditions have shown no excess of myeloma [133]. A nationwide study in Finland concluded that there was a twofold excess of multiple myeloma amongst all rheumatoid arthritis cases. This has been supported by a case-control study from Sweden. However, no such link has been found in other studies. Equally no excess for rheumatoid arthritis risk was found in US blacks or whites. These papers have failed to produce convincing evidence of aggregated or ‘total’ allergy, infection or vaccination patterns [132,133].

## References

[1] Adami J, Nyren O, Bergstrom R, Ekbom A, Engholm G, Englund A, Glimelius B. Smoking and the risk of leukemia, lymphoma, and multiple myeloma (Sweden). Cancer Causes Control 1998;9:49–56.

[2] Allan TM. ABO groups and myelomatosis. Br Med J 1970;4:178.

[3] Andersson M, Carstensen B, Visfeldt J. Leukemia and other related hematological disorders among Danish patients exposed to Thorotrast. Radiat Res 1993;134:224–33.

[4] Andersson M, Storm HH. Cancer incidence among Danish Thorotrast-exposed patients. J Natl Cancer Inst 1992;84:1318–25.

[5] Andjelkovich D, Taulbee J, Blum S. Mortality of female workers in rubber manufacturing plant. J Occup Med 1978;20:409–13.

[6] Axelsson U, Bachmann R, Hallen J. Frequency of pathological proteins (M-components) om 6,995 sera from an adult population. Acta Med Scand 1966;179:235–47.

[7] Beral V, Newton R. Overview of the epidemiology of immunodeficiency-associated cancers. J Natl Cancer Inst Monogr 1998:1–6.

[8] Bergsagel DE, Wong O, Bergsagel PL, Alexanian R, Anderson K, Kyle RA, Raabe GK. Benzene and multiple myeloma: appraisal of the scientific evidence. Blood 1999;94:1174–82.

[9] Berkheiser SW. Review of leukemia, lymphoma, and myeloma before and after the TMI accident. Pa Med 1986;89:50–2.

[10] Bertazzi A, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiology 1993;4:398–406.

[11] Bertazzi PA, Pesatori AC, Bernucci I, Landi MT, Consonni D. Dioxin exposure and human leukemias and lymphomas. Lessons from the Seveso accident and studies on industrial workers. Leukemia 1999;13(Suppl 1):S72–74.

[12] Bertazzi PA, Zocchetti C, Guercilena S, Consonni D, Tironi A, Landi MT, Pesatori AC. Dioxin exposure and cancer risk: a 15-year mortality study after the “Seveso accident”. Epidemiology 1997;8:646–52.

[13] Bethwaite PB, Pearce N, Fraser J. Cancer risks in painters: study based on the New Zealand Cancer Registry. Br J Ind Med 1990;47:742–6.

[14] Bezabeh S, Engel A, Morris CB, Lamm SH. Does benzene cause multiple myeloma? An analysis of the published case-control literature. Environ Health Perspect 1996;104(Suppl 6):1393–8.

[15] Bithell JF, Dutton SJ, Draper GJ, Neary NM. Distribution of childhood leukaemias and non-Hodgkin’s lymphomas near nuclear installations in England and Wales. BMJ 1994;309:501–5.

[16] Blade J, Lopez-Guillermo A, Rozman C, Cervantes F, Salgado C, Aguilar JL, Vives-Corrons JL, Montserrat E. Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. Br J Haematol 1992;81:391–4.

[17] Blair A, Hartge P, Stewart PA, McAdams M, Lubin J. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Med 1998;55:161–71.

[18] Blair A, Zahm SH. Agricultural exposures and cancer. Environ Health Perspect 1995;103(Suppl 8):205–8.

[19] Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni Jr JF. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health 1992;18:209–15.

[20] Blattner WA, Jacobson RJ, Shulman G. Multiple myeloma in South African blacks. Lancet 1979;1:928–9.

[21] Boffetta P, Stellman SD, Garfinkel L. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer 1989;43:554–9.

[22] Boice Jr JD, Day NE, Andersen A, Brinton LA, Brown R, Choi NW, Clarke EA, Coleman MP, Curtis RE, Flannery JT. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst 1985;74:955–75.

[23] Boice Jr JD, Morin MM, Glass AG, Friedman GD, Stovall M, Hoover RN, Fraumeni Jr JF. Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. JAMA 1991;265:1290–4.

[24] Bourguet CC, Grufferman S, Delzell E, DeLong ER, Cohen HJ. Multiple myeloma and family history of cancer. A case-control study. Cancer 1985;56:2133–9.

[25] Bowden M, Crawford J, Cohen HJ, Noyama O. A comparative study of monoclonal gammopathies and immunoglobulin levels in Japanese and United States elderly. J Am Geriatr Soc 1993;41:11–4.

[26] Brown LM, Burmeister LF, Everett GD, Blair A. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control 1993;4:153–6.

[27] Brown LM, Everett GD, Burmeister LF, Blair A. Hair dye use and multiple myeloma in white men. Am J Public Health 1992;82:1673–4.

[28] Brown LM, Everett GD, Gibson R, Burmeister LF, Schuman LM, Blair A. Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. Cancer Causes Control 1992;3:49–55.

[29] Brown LM, Gibson R, Burmeister LF, Schuman LM, Everett GD, Blair A. Alcohol consumption and risk of leukemia, non-Hodgkin's lymphoma, and multiple myeloma. Leuk Res 1992;16:979–84.

[30] Brown LM, Linet MS, Greenberg RS, Silverman DT, Hayes RB, Swanson GM, Schwartz AG, Schoenberg JB, Pottern LM, Fraumeni Jr JF. Multiple myeloma and family history of cancer among blacks and whites in the U.S. Cancer 1999;85:2385–90.

[31] Brugiatelli M, Comis M, Iacopino P, Morabito F, Nobile F, Trapani LV, Neri A. Multiple myeloma in husband and wife. Acta Haematol 1980;64:227–9.

[32] Caldwell GG, Kelley D, Zack M, Falk H, Heath Jr CW. Mortality and cancer frequency among military nuclear test (Smoky) participants, 1957 through 1979. JAMA 1983;250:620–4.

[33] Cartwright RA, Alexander FE, McKinney PA, Ricketts TJ. Leukaemia and lymphoma: an atlas of distribution within areas of England and Wales 1984–1988. London: Leukaemia Research Fund; 1990.

[34] Cartwright RA, McNally RJQ, Rowland DJ, Thomas J. The descriptive epidemiology of leukaemia and related conditions in parts of the United Kingdom 1984–1993. London: Leukaemia Research Fund; 1997.

[35] Cerhan JR, Cantor KP, Williamson K, Lynch CF, Torner JC, Burmeister LF. Cancer mortality among Iowa farmers: recent results, time trends, and lifestyle factors (United States). Cancer Causes Control 1998;9:311–9.

[36] Chatenoud L, Tavani A, La Vecchia C, Jacobs Jr DR, Negri E, Levi F, Franceschi S. Whole grain food intake and cancer risk. Int J Cancer 1998;77:24–8.

[37] Chiu BC, Cerhan JR, Folsom AR, Sellers TA, Kushi LH, Wallace RB, Zheng W, Potter JD. Diet and risk of non-Hodgkin lymphoma in older women. JAMA 1996;275:1315–21.

[38] Cocco P, Blair A, Congia P, Saba G, Ecca AR, Palmas C. Long-term health effects of the occupational exposure to DDT. A preliminary report. Ann NY Acad Sci 1997;837:246–56.

[39] Cohen HJ, Crawford J, Rao MK, Pieper CF, Currie MS. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. Am J Med 1998;104:439–44.

[40] Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality. IARC Sci Publ 1993:1–806.

[41] Comotti B, Bassan R, Buzzetti M, Finazzi G, Barbui T. Multiple myeloma in a pair of twins. Br J Haematol 1987;65:123–4.

[42] Cook-Mozaffari P, Darby S, Doll R. Cancer near potential sites of nuclear installations. Lancet 1989;2:1145–7.

[43] Correa A, Jackson L, Mohan A, Perry H, Helzlsouer K. Use of hair dyes, hematopoietic neoplasms, and lymphomas: a literature review. II. Lymphomas and multiple myeloma. Cancer Invest 2000;18:467–79.

[44] Crump KS. Risk of benzene-induced leukemia predicted from the Pliofilm cohort. Environ Health Perspect 1996;104(Suppl 6):1437–41.

[45] Cuzick J. Radiation-induced myelomatosis. N Engl J Med 1981;304:204–10.

[46] Cuzick J, De Stavola B. Multiple myeloma – a case-control study. Br J Cancer 1988;57:516–20.

[47] Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987;55:179–90.

[48] Darby SC, Kendall GM, Fell TP, O'Hagan JA, Muirhead CR, Ennis JR, Ball AM, Dennis JA, Doll R. A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. Br Med J (Clin Res Ed) 1988;296:332–8.

[49] Darby SC, Reeves G, Key T, Doll R, Stovall M. Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. Int J Cancer 1994;56:793–801.

[50] Davies FE, Rollinson SJ, Rawstron AC, Roman E, Richards S, Drayson M, Child JA, Morgan GJ. High-producer haplotypes of tumor necrosis factor alpha and lymphotoxin alpha are associated with an increased risk of myeloma and have an improved progression-free survival after treatment. J Clin Oncol 2000;18:2843–51.

[51] Davis FG, Boice Jr JD, Hrubec Z, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer Res 1989;49:6130–6.

[52] Delzell E, Monson RR. Mortality among rubber workers: X. Reclaim workers. Am J Ind Med 1985;7:307–13.

[53] Dement JM, Hensley L, Kieding S, Lipscomb H. Proportionate mortality among union members employed at three Texas refineries. Am J Ind Med 1998;33:327–40.

[54] Demers PA, Vaughan TL, Koepsell TD, Lyon JL, Swanson GM, Greenberg RS, Weiss NS. A case-control study of multiple myeloma and occupation. Am J Ind Med 1993;23:629–39.

[55] Divine BJ, Hartman CM. Mortality update of butadiene production workers. Toxicology 1996;113:169–81.

[56] Divine BJ, Hartman CM, Wendt JK. Update of the Texaco mortality study 1947–93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals. Occup Environ Med 1999;56:174–80.

[57] Doody MM, Linet MS, Glass AG, Friedman GD, Pottern LM, Boice Jr JD, Fraumeni Jr JF. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. Cancer Causes Control 1992;3:449–56.

[58] Doody MM, Mandel JS, Lubin JH, Boice Jr JD. Mortality among United States radiologic technologists, 1926–90. Cancer Causes Control 1998;9:67–75.

[59] Dosemeci M, Yin SN, Linet M, Wacholder S, Rothman N, Li GL, Chow WH, Wang YZ, Jiang ZL, Dai TR, Zhang WU, Chao XJ, Ye PZ, Kou QR, Fan YH, Zhang XC, Lin XF, Meng JF, Zho JS, Blot WJ, Hayes RB. Indirect validation of benzene exposure assessment by association with benzene poisoning. Environ Health Perspect 1996;104(Suppl 6):1343–7.

[60] Dring AM, Davies FE, Rollinson SJ, Roddam PL, Rawstron AC, Child JA, Jack AS, Morgan GJ. Interleukin 6, tumour necrosis factor alpha and lymphotoxin polymorphisms in monoclonal gammopathy of uncertain significance and multiple myeloma. Br J Haematol 2001;112:249–50.

[61] Ende M. Multiple myeloma: a cluster in Virginia? Va Med 1979;106:115–6.

[62] Eriksson M. Rheumatoid arthritis as a risk factor for multiple myeloma: a case-control study. Eur J Cancer 1993;29A:259–63.

[63] Eriksson M, Hallberg B. Familial occurrence of hematologic malignancies and other diseases in multiple myeloma: a case-control study. Cancer Causes Control 1992;3:63–7.

[64] Eriksson M, Hardell L, Malker H, Weiner J. Malignant lymphoproliferative diseases in occupations with potential exposure to phenoxyacetic acids or dioxins: a register-based study. Am J Ind Med 1992;22:305–12.

[65] Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: a population based case-control study. Br J Ind Med 1992;49:95–103.

[66] Fester J, Marrink J, Sijpesteijn J. A study on the association between myelomatosis and immunoglobulin all types, HLA, and blood groups. Immunogen 1976;3:201.

[67] Figgs LW, Dosemeci M, Blair A. Risk of multiple myeloma by occupation and industry among men and women: a 24-state death certificate study. J Occup Med 1994;36:1210–21.

[68] Finch S. Leukaemia and lymphoma in atomic bomb survivors. In: Boice Jr JD, Fraumeni Jr JF, editors. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press; 1984. p. 37–44.

[69] Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. N Engl J Med 1991;324:212–8.

[70] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369–76.

[71] Flodin U, Fredriksson M, Persson B. Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-referent study. Am J Ind Med 1987;12:519–29.

[72] Fox AJ, Collier PF. A survey of occupational cancer in the rubber and cablemaking industries: analysis of deaths occurring in 1972–74. Br J Ind Med 1976;33:249–64.

[73] Friedman GD. Multiple myeloma: relation to propoxyphene and other drugs, radiation and occupation. Int J Epidemiol 1986;15:424–6.

[74] Friedman GD. Cigarette smoking, leukemia, and multiple myeloma. Ann Epidemiol 1993;3:425–8.

[75] Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. Int J Cancer 1996;67:498–503.

[76] Fu H, Demers PA, Costantini AS, Winter P, Colin D, Kogevinas M, Boffetta P. Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. Occup Environ Med 1996;53:394–8.

[77] Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH. Allergies and agricultural exposure as risk factors for multiple myeloma. Br J Cancer 1983;48:853–7.

[78] Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ 1990;300:423–9.

[79] Gibson R, Graham S, Lilienfeld A, Schuman L, Dowd JE, Levin ML. Irradiation in the epidemiology of leukemia among adults. J Natl Cancer Inst 1972;48:301–11.

[80] Gilbert ES, Marks S. An analysis of the mortality of workers in a nuclear facility. Radiat Res 1979;79:122–48.

[81] Gilbert ES, Omohundro E, Buchanan JA, Holter NA. Mortality of workers at the Hanford site: 1945–1986. Health Phys 1993;64:577–90.

[82] Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945–1981. Health Phys 1989;56:11–25.

[83] Goedert JJ, Cote TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, Jaffe ES, Biggar RJ. Spectrum of AIDS-associated malignant disorders. Lancet 1998;351:1833–9.

[84] Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994;86:1600–8.

[85] Goldstein BD, Shalat SL. The casual relation between benzene exposure and multiple myeloma. Blood 2000;95:1512–4.

[86] Gramenzi A, Buttino I, D'Avanzo B, Negri E, Franceschi S, La Vecchia C. Medical history and the risk of multiple myeloma. Br J Cancer 1991;63:769–72.

[87] Gregersen H, Mellemkjaer L, Salling IJ, Sorensen HT, Olsen JH, Pedersen JO, Dahlerup JF. Cancer risk in patients with monoclonal gammopathy of undetermined significance. Am J Hematol 2000;63:1–6.

[88] Griem ML, Kleinerman RA, Boice Jr JD, Stovall M, Shefner D, Lubin JH. Cancer following radiotherapy for peptic ulcer. J Natl Cancer Inst 1994;86:842–9.

[89] Grosbois B, Jego P, Attal M, Payen C, Rapp MJ, Fuzibet JG, Maigre M, Bataille R. Familial multiple myeloma: report of fifteen families. Br J Haematol 1999;105:768–70.

[90] Grufferman S, Cohen HJ, Delzell ES, Morrison MC, Schold Jr SC, Moore JO. Familial aggregation of multiple myeloma and central nervous system diseases. J Am Geriatr Soc 1989;37:303–9.

[91] Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. AIDS 1999;13:839–43.

[92] Gustavsson P, Hogstedt C, Holmberg B. Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scand J Work Environ Health 1986;12:538–44.

[93] Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li CY, Rothman N, Hoover RN, Linet MS. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group. J Natl Cancer Inst 1997;89:1065–71.

[94] Heineman EF, Zahm SH, McLaughlin JK, Vaught JB, Hrubec Z. A prospective study of tobacco use and multiple myeloma: evidence against an association. Cancer Causes Control 1992;3:31–6.

[95] Herrinton LJ. The epidemiology of monoclonal gammopathy of unknown significance: a review. Curr Top Microbiol Immunol 1996;210:389–95.

[96] Herrinton LJ, Demers PA, Koepsell TD, Weiss NS, Daling JR, Taylor JW, Lyon JL, Swanson GM, Greenberg RS. Epidemiology of the M-component immunoglobulin types of multiple myeloma. Cancer Causes Control 1993;4:83–92.

[97] Herrinton LJ, Weiss NS, Koepsell TD, Daling JR, Taylor JW, Lyon JL, Swanson GM, Greenberg RS. Exposure to hair-coloring products and the risk of multiple myeloma. Am J Public Health 1994;84:1142–4.

[98] Herrinton LJ, Weiss NS, Olshan AF. Epidemiology of multiple myeloma. In: Malpas JP, Bergsagel DE, Kyle RA, editors. Myeloma-biology and management. Oxford, England: Oxford University Press; 1995. p. 1127–41.

[99] Herrinton LJ, Weiss NS, Olshan AF. Multiple myeloma. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996. p. 946–70.

[100] Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, Cederquist E, Ericsson UB, Hallquist A, Larsson LG. Cancer risk after iodine-131 therapy for hyperthyroidism. J Natl Cancer Inst 1991;83:1072–7.

[101] Huebner WW, Schnatter AR, Nicolich MJ, Jorgensen G. Mortality experience of a young petrochemical industry cohort. 1979–1992 follow-up study of US-based employees. J Occup Environ Med 1997;39:970–82.

[102] Ichimaru M, Ishimaru T, Belsky JL. Incidence of leukemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki, 1950–71. Radiation dose, years after exposure, age at exposure, and type of leukemia. J Radiat Res (Tokyo) 1978;19:262–82.

[103] Ichimaru M, Ishimaru T, Mikami M, Matsunaga M. Multiple myeloma among atomic bomb survivors in Hiroshima and Nagasaki, 1950–76: relationship to radiation dose absorbed by marrow. J Natl Cancer Inst 1982;69:323–8.

[104] Inskip PD, Kleinerman RA, Stovall M, Cookfair DL, Hadjimichael O, Moloney WC, Monson RR, Thompson WD, Wactawski-Wende J, Wagoner JK. Leukemia, lymphoma, and multiple myeloma after pelvic radiotherapy for benign disease. Radiat Res 1993;135:108–24.

[105] Inskip PD, Monson RR, Wagoner JK, Stovall M, Davis FG, Kleinerman RA, Boice Jr JD. Leukemia following radiotherapy for uterine bleeding. Radiat Res 1990;122:107–19.

[106] Ireland B, Collins JJ, Buckley CF, Riordan SG. Cancer mortality among workers with benzene exposure. Epidemiology 1997;8:318–20.

[107] Isobe T, Osserman EF. Pathologic conditions associated with plasma cell dyscrasias: a study of 806 cases. Ann NY Acad Sci 1971;190:507–18.

[108] Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis 1978;31:691–6.

[109] Jablon S, Miller RW. Army technologists: 29-year follow up for cause of death. Radiology 1978;126:677–9.

[110] Jensen OM. Cancer morbidity and causes of death among Danish brewery workers. Int J Cancer 1979;23:454–63.

[111] Johnston JM, Grufferman S, Bourguet CC, Delzell E, DeLong ER, Cohen HJ. Socioeconomic status and risk of multiple myeloma. J Epidemiol Community Health 1985;39:175–8.

[112] Judson IR, Wiltshaw E, Newland AC. Multiple myeloma in a pair of monozygotic twins: the first reported case. Br J Haematol 1985;60:551–4.

[113] Kanoh T. Multiple myeloma in spouses. Eur J Haematol 1988;41:397.

[114] Kanoh T, Ohno T, Usui T, Inamoto Y. Multiple myeloma in husband and wife. Nippon Ketsueki Gakkai Zasshi 1989;52:763–6.

[115] Katusic S, Beard CM, Kurland LT, Weis JW, Bergstralh E. Occurrence of malignant neoplasms in the Rochester, Minnesota, rheumatoid arthritis cohort. Am J Med 1985;78:50–5.

[116] Keshava-Prasad HS, Prangnell DR, Adelman MI. Multiple myeloma in spouses. Clin Lab Haematol 1996;18:61–2.

[117] Khuder SA, Mutgi AB. Meta-analyses of multiple myeloma and farming. Am J Ind Med 1997;32:510–6.

[118] Koepsell TD, Daling JR, Weiss NS, Taylor JW, Olshan AF, Lyon JL, Swanson GM, Child M. Antigenic stimulation and the occurrence of multiple myeloma. Am J Epidemiol 1987;126:1051–62.

[119] Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol 1997;145:1061–75.

[120] Kogevinas M, Ferro G, Saracci R, Andersen A, Biocca M, Coggon D, Gennaro V, Hutchings S, Kolstad H, Lundberg I. Cancer mortality in an international cohort of workers exposed to styrene. IARC Sci Publ 1993:289–300.

[121] Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med 1998;55:1–12.

[122] Kosaka M, Okagawa K, Miyamoto Y, Goto T, Saito S. Geographic clustering of myeloma in Tokushima. Int J Hematol 1991;54:405–9.

[123] Kristensen P, Andersen A, Irgens LM, Laake P, Bye AS. Incidence and risk factors of cancer among men and women in Norwegian agriculture. Scand J Work Environ Health 1996;22:14–26.

[124] Kyle RA. "Benign" monoclonal gammopathy–after 20 to 35 years of follow-up. Mayo Clin Proc 1993;68:26–36.

[125] Kyle RA, Finkelstein S, Elveback LR, Kurland LT. Incidence of monoclonal proteins in a Minnesota community with a cluster of multiple myeloma. Blood 1972;40:719–24.

[126] Kyle RA, Greipp PR. Multiple myeloma. Houses and spouses. Cancer 1983;51:735–9.

[127] Kyle RA, Heath Jr CW, Carbone P. Multiple myeloma in spouses. Arch Intern Med 1971;127:944–6.

[128] Kyle RA, Herber L, Evatt BL, Heath Jr CW. Multiple myeloma. A community cluster. JAMA 1970;213:1339–41.

[129] Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance. Hematol Oncol Clin North Am 1999;13:1181–202.

[130] Lewis DR, Pottern LM, Brown LM, Silverman DT, Hayes RB, Schoenberg JB, Greenberg RS, Swanson GM, Schwartz AG, Liff JM. Multiple myeloma among blacks and whites in the United States: the role of chronic antigenic stimulation. Cancer Causes Control 1994;5:529–39.

[131] Lewis EB. Leukaemia, multiple myeloma and aplastic anemia in American radiologists. Science 1963;142:1492–4.

[132] Linet MS. Is chronic antigenic stimulation etiologically related to multiple myeloma? In: Obrams GI, Potter M, editors. Epidemiology and biology of multiple myeloma. Berlin: Springer; 1991. p. 99–105.

[133] Linet MS, Harlow SD, McLaughlin JK. A case-control study of multiple myeloma in whites: chronic antigenic stimulation, occupation, and drug use. Cancer Res 1987;47:2978–81.
[134] Linet MS, McLaughlin JK, Harlow SD, Fraumeni JF. Family history of autoimmune disorders and cancer in multiple myeloma. Int J Epidemiol 1988;17:512–3.
[135] Little MP, Weiss HA, Boice Jr JD, Darby SC, Day NE, Muirhead CR. Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. Radiat Res 1999;152:280–92.
[136] Lopez-Abente G, Aragones N, Pollan M, Ruiz M, Gandarillas A. Leukemia, lymphomas, and myeloma mortality in the vicinity of nuclear power plants and nuclear fuel facilities in Spain. Cancer Epidemiol Biomarkers Prev 1999;8:925–34.
[137] Ludwig H, Mayr W. Genetic aspects of susceptibility to multiple myeloma. Blood 1982;59:1286–91.
[138] Lundberg I, Milatou-Smith R. Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand J Work Environ Health 1998;24:270–5.
[139] Mancuso TF, Stewart A, Kneale G. Radiation exposures of Hanford workers dying from cancer and other causes. Health Phys 1977;33:369–85.
[140] Martling U, Mattsson A, Travis LB, Holm LE, Hall P. Mortality after long-term exposure to radioactive Thorotrast: a forty- year follow-up survey in Sweden. Radiat Res 1999;151:293–9.
[141] Massoudi BL, Talbott EO, Day RD, Swerdlow SH, Marsh GM, Kuller LH. A case-control study of hematopoietic and lymphoid neoplasms: the role of work in the chemical industry. Am J Ind Med 1997;31:21–7.
[142] McLaughlin JK, Malker HS, Linet MS, Ericsson J, Stone BJ, Weiner J, Blot WJ, Fraumeni Jr JF. Multiple myeloma and occupation in Sweden. Arch Environ Health 1988;43:7–10.
[143] Metayer C, Johnson ES, Rice JC. Nested case-control study of tumors of the hemopoietic and lymphatic systems among workers in the meat industry. Am J Epidemiol 1998;147:727–38.
[144] Milham Jr S. Leukemia and multiple myeloma in farmers. Am J Epidemiol 1971;94:507–10.
[145] Miller RW. Deaths from childhood leukemia and solid tumors among twins and other sibs in the United States, 1960–67. J Natl Cancer Inst 1971;46:203–9.
[146] Mills PK, Newell GR, Beeson WL, Fraser GE, Phillips RL. History of cigarette smoking and risk of leukemia and myeloma: results from the Adventist health study. J Natl Cancer Inst 1990;82:1832–6.
[147] Monson RR, Nakano KK. Mortality among rubber workers. II. Other employees. Am J Epidemiol 1976;103:297–303.
[148] Morgan RW, Claxton KW, Divine BJ, Kaplan SD, Harris VB. Mortality among ethylene oxide workers. J Occup Med 1981;23:767–70.
[149] Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, O'Hagan JA, Thomas JM, Kendall GM, Silk TJ, Bingham D, Berridge GL. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. J Radiol Prot 1999;19:3–26.
[150] Nandakumar A, Armstrong BK, de Klerk NH. Multiple myeloma in Western Australia: a case-control study in relation to occupation, father's occupation, socioeconomic status and country of birth. Int J Cancer 1986;37:223–6.
[151] Neriishi K, Yoshimoto Y, Carter RL, Matsuo T, Ichimaru M, Mikami M, Abe T, Fujimura K, Kuramoto A. Monoclonal gammopathy in atomic bomb survivors. Radiat Res 1993;133:351–9.
[152] Nilsson RI, Nordlinder R, Horte LG, Jarvholm B. Leukaemia, lymphoma, and multiple myeloma in seamen on tankers. Occup Environ Med 1998;55:517–21.
[153] Nishiyama H, Anderson RE, Ishimaru T, Ishida K, Ii Y, Okabe N. The incidence of malignant lymphoma and multiple myeloma in Hiroshima and Nagasaki atomic bomb survivors, 1945–1965. Cancer 1973;32:1301–9.
[154] Parkin DM, Muir CS. Cancer incidence in five continents. Comparability and quality of data. IARC Sci Publ 1992:45–173.
[155] Pasqualetti P, Casale R. Risk of malignant transformation in patients with monoclonal gammopathy of undetermined significance. Biomed Pharmacother 1997;51:74–8.
[156] Pearce N, Prior I, Methven D, Culling C, Marshall S, Auld J, de Boer G, Bethwaite P. Follow up of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific. BMJ 1990;300:1161–6.
[157] Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA. Case-control study of multiple myeloma and farming. Br J Cancer 1986;54:493–500.
[158] Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. Radiat Res 1996;146:1–27.
[159] Pietruszka M, Rabin BS, Srodes C. Letter: multiple myeloma in husband and wife. Lancet 1976;1:314.
[160] Polednak AP, Stehney AF, Rowland RE. Mortality among women first employed before 1930 in the U.S. radium dial-painting industry. A group ascertained from employment lists. Am J Epidemiol 1978;107:179–95.
[161] Potter M, Morrison S, Wiener F, Zhang XK, Miller FW. Induction of plasmacytomas with silicone gel in genetically susceptible strains of mice. J Natl Cancer Inst 1994;86:1058–65.
[162] Pottern LM, Gart JJ, Nam JM, Dunston G, Wilson J, Greenberg R, Schoenberg J, Swanson GM, Liff J, Schwartz AG. HLA and multiple myeloma among black and white men: evidence of a genetic association. Cancer Epidemiol Biomarkers Prev 1992;1:177–82.
[163] Pottern LM, Heineman EF, Olsen JH, Raffn E, Blair A. Multiple myeloma among Danish women: employment history and workplace exposures. Cancer Causes Control 1992;3:427–32.
[164] Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Matsui T. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994;137:S68–97.
[165] Preston DL, Pierce DA. The effect of changes in dosimetry on cancer mortality risk estimates in the atomic bomb survivors. Radiat Res 1988;114:437–66.
[166] Pukkala E, Notkola V. Cancer incidence among Finnish farmers, 1979–93. Cancer Causes Control 1997;8:25–33.
[167] Raabe GK, Collingwood KW, Wong O. An updated mortality study of workers at a petroleum refinery in Beaumont, Texas. Am J Ind Med 1998;33:61–81.
[168] Rettig MB, Ma HJ, Vescio RA, Pold M, Schiller G, Belson D, Savage A, Nishikubo C, Wu C, Fraser J, Said JW, Berenson JR. Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients. Science 1997;276:1851–4.
[169] Riedel DA, Pottern LM. The epidemiology of multiple myeloma. Hematol Oncol Clin North Am 1992;6:225–47.
[170] Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg LX, Edwards BK. SEER Cancer Statistics Review, 1973–1997. U.S. DHHS, PHS, NIH, Publ No. 00 2000:2789.
[171] Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 1987;316:1044–50.
[172] Ron E, Modan B, Boice Jr JD. Mortality after radiotherapy for ringworm of the scalp. Am J Epidemiol 1988;127:713–25.

[173] Ron E, Preston DL, Mabuchi K, Thompson DE, Soda M. Cancer incidence in atomic bomb survivors. Part IV: comparison of cancer incidence and mortality. Radiat Res 1994;137:S98–S112.
[174] Saleun JP, Vicariot M, Deroff P, Morin JF. Monoclonal gammopathies in the adult population of Finistere, France. J Clin Pathol 1982;35:63–8.
[175] Saracci R, Kogevinas M, Bertazzi PA, Bueno de Mesquita BH, Coggon D, Green LM, Kauppinen T, L'Abbe KA, Littorin M, Lynge E. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 1991;338:1027–32.
[176] Sathiakumar N, Delzell E, Hovinga M, Macaluso M, Julian JA, Larson R, Cole P, Muir DC. Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med 1998;55:230–5.
[177] Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med 1997;31:287–95.
[178] Schechter GP, Shoff N, Chan C. The frequency of monoclonal gammopathy of unknown significance in Black and Caucasian veterans in a hospital population. In: Obrams GI, Potter M, editors. Epidemiology and biology of multiple myeloma. New York: Springer; 1991. p. 83–5.
[179] Schnatter AR, Armstrong TW, Nicolich MJ, Thompson FS, Katz AM, Huebner WW, Pearlman ED. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. Occup Environ Med 1996;53:773–81.
[180] Schnatter AR, Armstrong TW, Thompson LS, Nicolich MJ, Katz AM, Huebner WW, Pearlman ED. The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. Environ Health Perspect 1996;104(Suppl 6):1375–9.
[181] Schnatter AR, Theriault G, Katz AM, Thompson FS, Donaleski D, Murray N. A retrospective mortality study within operating segments of a petroleum company. Am J Ind Med 1992;22:209–29.
[182] Schwartz GG. Multiple myeloma: clusters, clues, and dioxins. Cancer Epidemiol Biomarkers Prev 1997;6:49–56.
[183] Seltser R, Sartwell PE. The influence of occupational exposure to radiation on the mortality of American radiologists and other medical specialists. Am J Epidemiol 1965;81:2–22.
[184] Shimizu Y, Schull WJ, Kato H. Cancer risk among atomic bomb survivors. The RERF Life Span Study. Radiation Effects Research Foundation. JAMA 1990;264:601–4.
[185] Shore RE, Albert RE, Pasternack BS. Follow-up study of patients treated by X-ray epilation for Tinea capitis;resurvey of post-treatment illness and mortality experience. Arch Environ Health 1976;31:21–8.
[186] Shpilberg O, Modan M, Modan B, Chetrit A, Fuchs Z, Ramot B. Familial aggregation of haematological neoplasms: a controlled study. Br J Haematol 1994;87:75–80.
[187] Shulman G, Jacobson RJ. Immunocytoma in black and white South Africans. Trop Geogr Med 1980;32:112–7.
[188] Simmons Z, Albers JW, Bromberg MB, Feldman EL. Long-term follow-up of patients with chronic inflammatory demyelinating polyradiculoneuropathy, without and with monoclonal gammopathy. Brain 1995;118(Pt 2):359–68.
[189] Singh J, Dudley Jr AW, Kulig KA. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. J Lab Clin Med 1990;116:785–9.
[190] Smith PG, Doll R. Late effects of x irradiation in patients treated for metropathia haemorrhagica. Br J Radiol 1976;49:224–32.
[191] Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. Br Med J (Clin Res Ed) 1986;293:845–54.
[192] Spinelli JJ, Gallagher RP, Band PR, Threlfall WJ. Multiple myeloma, leukemia, and cancer of the ovary in cosmetologists and hairdressers. Am J Ind Med 1984;6:97–102.
[193] Stebbings JH, Lucas HF, Stehney AF. Mortality from cancers of major sites in female radium dial workers. Am J Ind Med 1984;5:435–59.
[194] Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Natl Cancer Inst 1999;91:779–86.
[195] Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S. Mortality among workers exposed to ethylene oxide. N Engl J Med 1991;324:1402–7.
[196] Steineck G, Wiklund K. Multiple myeloma in Swedish agricultural workers. Int J Epidemiol 1986;15:321–5.
[197] Svensson BG, Mikoczy Z, Stromberg U, Hagmar L. Mortality and cancer incidence among Swedish fishermen with a high dietary intake of persistent organochlorine compounds. Scand J Work Environ Health 1995;21:106–15.
[198] Teta MJ, Walrath J, Meigs JW, Flannery JT. Cancer incidence among cosmetologists. J Natl Cancer Inst 1984;72:1051–7.
[199] Tisdale JF, Stewart AK, Dickstein B, Little RF, Dube I, Cappe D, Dunbar CE, Brown KE. Molecular and serological examination of the relationship of human herpesvirus 8 to multiple myeloma: orf 26 sequences in bone marrow stroma are not restricted to myeloma patients and other regions of the genome are not detected. Blood 1998;92:2681–7.
[200] UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). Sources, effects and risks of ionizing radiation. New York: United Nations; 1988. p. 29–293.
[201] UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). Sources and effects of ionizing radiation. New York: United Nations Publ No E.94.IX.11; 1994. p. 11–183.
[202] UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). Sources and effects of ionizing radiation. New York: United Nations Publ No E.00.IX.3; 2000. p. 297–431.
[203] Van Kaick G, Dalheimer A, Hornik S, Kaul A, Liebermann D, Luhrs H, Spiethoff A, Wegener K, Wesch H. The german thorotrast study: recent results and assessment of risks. Radiat Res 1999;152:S64–71.
[204] Velez R, Beral V, Cuzick J. Increasing trends of multiple myeloma mortality in England and Wales; 1950–79: are the changes real? J Natl Cancer Inst 1982;69:387–92.
[205] Wang JX, Boice Jr JD, Li BX, Zhang JY, Fraumeni Jr JF. Cancer among medical diagnostic x-ray workers in China. J Natl Cancer Inst 1988;80:344–50.
[206] Wang JX, Inskip PD, Boice Jr JD, Li BX, Zhang JY, Fraumeni Jr JF. Cancer incidence among medical diagnostic X-ray workers in China, 1950 to 1985. Int J Cancer 1990;45:889–95.
[207] Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer 1994;59:327–38.
[208] Wiklund K, Dich J. Cancer risks among male farmers in Sweden. Eur J Cancer Prev 1995;4:81–90.
[209] Wiklund K, Holm LE. Trends in cancer risks among Swedish agricultural workers. J Natl Cancer Inst 1986;77:657–64.
[210] Wilcosky TC, Checkoway H, Marshall EG, Tyroler HA. Cancer mortality and solvent exposures in the rubber industry. Am Ind Hyg Assoc J 1984;45:809–11.
[211] Williams AR, Weiss NS, Koepsell TD, Lyon JL, Swanson GM. Infectious and noninfectious exposures in the etiology of light chain myeloma: a case-control study. Cancer Res 1989;49:4038–41.
[212] Wong O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 1995;52:380–4.

[213] Wong O, Raabe GK. Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. Regul Toxicol Pharmacol 1997;26:188–99.

[214] Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. Occup Environ Med 1994;51:386–96.

[215] Wongsrichanalai C, Delzell E, Cole P. Mortality from leukemia and other diseases among workers at a petroleum refinery. J Occup Med 1989;31:106–11.

[216] Yin SN, Li GL, Tain FD, Fu ZI, Jin C, Chen YJ, Luo SJ, Ye PZ, Zhang JZ, Wang GC. Leukaemia in benzene workers: a retrospective cohort study. Br J Ind Med 1987;44:124–8.

[217] Yin SN, Li GL, Tain FD, Fu ZI, Jin C, Chen YJ, Luo SJ, Ye PZ, Zhang JZ, Wang GC. A retrospective cohort study of leukemia and other cancers in benzene workers. Environ Health Perspect 1989;82:207–13.

[218] Yin SN, Linet MS, Hayes RB, Li GL, Dosemeci M, Wang YZ, Chow WH, Jiang ZL, Wacholder S, Zhang WU. Cohort study among workers exposed to benzene in China: I. General methods and resources. Am J Ind Med 1994;26:383–400.

[219] Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Blair A. Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. Am J Public Health 1992;82:990–7.

[220] Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, Bjorkholm M, Holm G, Yi Q. Interleukin 6, tumour necrosis factor alpha, interleukin 1beta and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. Br J Haematol 2000;109:39–45.

[221] Zheng TZ, Mayne ST, Flannery J. The time trends of multiple myeloma in Connecticut, 1935–1987. Int J Cancer 1992;50:163–4.